

# DECISION SUPPORT TOOL FOR PENICILLIN-RELATED ALLERGIES

The present tool is preferably intended for health professionals who are not specialized in allergy. The information is for reference purposes and therefore does not replace the judgment of the professional and should be used only as a decision aid. The tool, developed through a systematic approach, is supported by the scientific literature as well as by the experiential knowledge of Quebec experts. For more details, click [here](#).

## REMEMBER THAT...

- Real penicillin allergies are infrequent. For more information click [here](#);
- Some viral infections combined with an antibiotic intake (e.g., amoxicillin) result in cutaneous eruptions that may be misleading for allergy diagnostics, especially in children;
- Too many patients are falsely labeled as “allergic” to penicillins and this may lead to the prescription of broad-spectrum antibiotics that trigger more adverse effects.

## KEY ELEMENTS TO IDENTIFY & EVALUATE THE SEVERITY OF THE INITIAL REACTION

IDENTIFY & EVALUATE

- What is the patient’s **allergy status**?
- What was the **antibiotic** of the class of penicillins that could be involved?
- How much time** has elapsed between the antibiotics intake and the reaction?
- What were the **key clinical manifestations**, symptoms or impairments observed?
  - in case of a cutaneous manifestations, how was the **severity**?
  - did the reaction have any others **severity criteria**?

- Any element of the clinical history that suggests the possibility of an immediate or severe delayed reaction requires an extra level of vigilance when re-administering a beta-lactam.
- In the presence of severity criteria (e.g., an organ or mucosal impairment, desquamation, etc.), it is advisable to obtain consultation with **specialized services**.

## DECISION MAKING REGARDING THE ADMINISTRATION OF A NEW BETA-LACTAM

TO CHOOSE

- What are the elements to consider when re-administering a beta-lactam?

- The probability that the initial reaction is of an allergic nature and the severity of it;
- The **risk of cross reaction** between the indicated beta-lactam and the penicillin concerned, which may increase when the two antibiotics share **SIMILAR** structural and physicochemical properties (Table 1).

### Structural and physicochemical properties of beta-lactams

**Table 1.**  
SIMILAR to the penicillins properties<sup>†</sup>

Cefadroxil [1 <sup>st</sup> ] R1 100% Amoxicillin
Cephalexin [1 <sup>st</sup> ] R1 100% Ampicillin
Cefprozil [2 <sup>nd</sup> ] R1 100% Amoxicillin
*Cefaclor [2 <sup>nd</sup> ] R1 100% Ampicillin
Cefoxitin [2 <sup>nd</sup> ]

**Table 2.**  
DIFFERENT from the penicillins properties<sup>‡</sup>

Cefazolin [1 <sup>st</sup> ]	Ceftriaxone [3 <sup>rd</sup> ]
Cefuroxime [2 <sup>nd</sup> ]	Cefepime [4 <sup>th</sup> ]
Cefotaxime [3 <sup>rd</sup> ]	Meropenem
Ceftazidime [3 <sup>rd</sup> ]	Imipenem
Cefixime [3 <sup>rd</sup> ]	Ertapenem

- Can I prescribe a beta-lactam? If yes, what would be the **conditions of administration**?

- Engage the patient or his family in the decision.

## PATIENT MONITORING AFTER THE ADMINISTRATION OF THE NEW BETA-LACTAM

TO NOTE

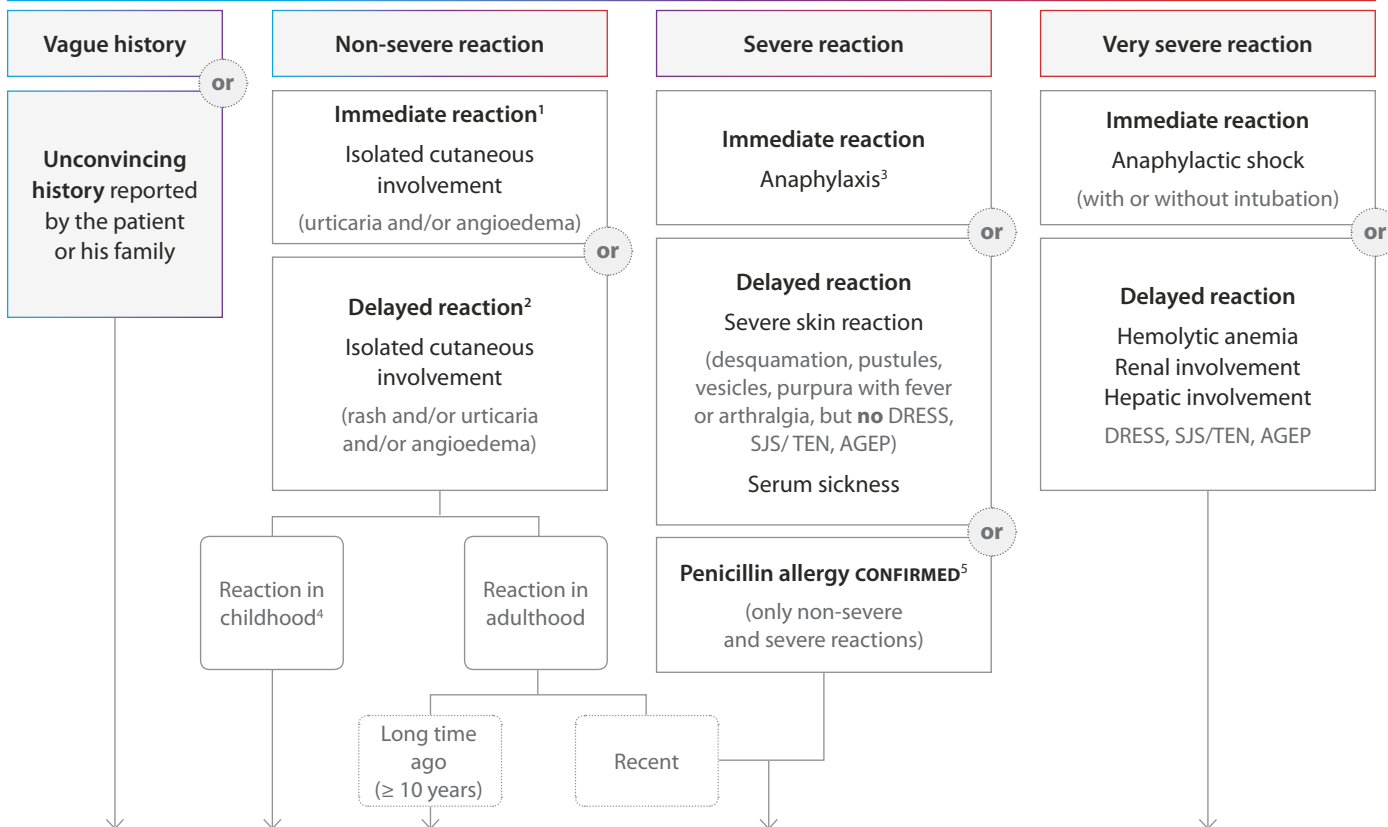
- What are the **actions** to be taken after the administration of the new beta-lactam in case of penicillin allergy?

- Clearly document the reaction (allergic reaction or antibiotic tolerance);
- If allergic reaction, complete the declaration **form** for a new drug allergy reaction.

**Legend :** † = penicillins G and V, amoxicillin and ampicillin; ‡ = include the previously mentioned penicillins in addition to cloxacillin and piperacillin;  
\* = The cefaclor is discontinued in Canada; R1 100 % = cephalosporin having an R1 side chain 100 % identical with that of ampicillin or amoxicillin;  
[1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>] = generation of cephalosporins.

## SEVERITY OF THE PREVIOUS REACTION

ASSESS THE SEVERITY OF THE INITIAL REACTION



DECISION MAKING CONCERNING THE CHOICE OF BETA-LACTAM AND CONDITIONS OF ADMINISTRATION

**I PRESCRIBE SAFELY**

- 👍 Carbapenems<sup>6</sup>
- 👍 Cephalosporins **DIFFERENT\***
- 👍 Cephalosporins **SIMILAR\*** if the history of allergy does not suggest an immediate reaction...

↓

**If in doubt about the possibility of an immediate reaction...**

An observation period of one hour after the administration of the first dose under the supervision of a health professional could be advised according to the clinician's judgement.

**I PRESCRIBE WITH CAUTION**

- 👉 Penicillines

The 1<sup>st</sup> dose should **always** be administered under medical supervision.

**If history of :**

- **Immediate reactions** - a drug provocation test should be performed;
- **Delayed reactions** - the patient or his family should be advised about the risk of using the antibiotics.

**I PRESCRIBE WITH CAUTION**

- 👉 Carbapenems<sup>6</sup>
- 👉 Cephalosporines **DIFFERENT\***
- 👉 Cephalosporines **SIMILAR\*** *only* for antecedents of recent non-severe reactions in adults **or** for serum sickness-like reactions in children<sup>4</sup>.

The 1<sup>st</sup> dose should **always** be administered under medical supervision.

**If history of :**

- **Immediate reactions** - a drug provocation test should be performed;
- **Delayed reactions** - the patient or his family should be advised about the risk of possible recurrence within days of using the antibiotics.

**I AVOID PRESCRIBING**

- 🚫 Penicillines
- 🚫 Cephalosporins **SIMILAR\*** for any other clinical situation (except for history of recent non-severe adult reactions **or** serum sickness-like reactions in children<sup>4</sup>, as described above).

**I AVOID PRESCRIBING**

- 🚫 Beta-lactam

**Privilege another class of antibiotic.**

If strong indication of a beta-lactam, obtain a consultation with specialized services.

\* For more information on similar cephalosporins and different penicillins, see [Tables 1 and 2](#).



For more information on clinical manifestations, see the [interactive tool](#).

1. Immediate reaction (type I or IgE-mediated): usually occurs within one hour after taking the **first dose** of an antibiotic.
2. Delayed reaction (types II, III and IV): may occur at any time from one hour after administration of a drug.
3. Anaphylaxis without shock or intubation: requires an extra level of vigilance.
4. Delayed skin reactions and serum sickness-like reactions that occur in children on antibiotic therapy are generally non-allergic and may be of viral origin.
5. Without recommendations for other beta-lactams.
6. Use sparingly with increasing prevalence of carbapenemase-producing enterobacteria.

## 1. WHAT IS THE ALLERGY STATUS OF THE PATIENT?

### Penicillin allergy is **CONFIRMED...**

If valid and compliant diagnostic tests (skin test or drug provocation test) have been performed by a doctor.

### Penicillin allergy is **SUSPECTED...**

If a patient reports a history of penicillin allergy that has never been confirmed by diagnostic tests.



#### REMEMBER THAT...

- Atopy and food allergies are not risk factors for drug allergy;
- People with a family history of drug allergy are no more likely to respond in their turn to the concerned drugs.



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## 2. WHAT WAS ANTIBIOTICS OF THE CLASS OF PENICILLINS THAT MAY BE CONCERNED?



### IDENTIFY...

The antibiotic (s) suspected or evoked by the patient:

- What was the name of the antibiotic that could be concerned?
- What was the dose, route of administration and duration of treatment?



### VERIFY IF...

- Since the so-called allergic episode the patient has resumed taking without problem and without reaction:
  - **the same antibiotic:** so he is not allergic to this antibiotic;
  - **another antibiotic in the penicillin class:** this does not exclude the possibility that he is still allergic to the antibiotic that caused the initial reaction (e.g., a patient may be allergic to piperacillin/tazobactam, but tolerate amoxicillin).
- The patient has already undergone allergy testing (skin test or drug provocation test) for the concerned penicillin or for another beta-lactam.



### CAUTION

In patients with a chronic disease and who are frequently exposed to antibiotics (e.g., those with cystic fibrosis), a higher level of alertness than the general population should be maintained since this is an important risk factor for the development of a drug allergy, especially to beta-lactams.



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## 3. HOW MUCH TIME HAS ELAPSED BETWEEN THE ANTIBIOTIC INTAKE AND THE REACTION?



## IDENTIFY...

## The chronology of the obtained reaction:

- In the patient's recollection, how old he was at the moment of reaction?
- How much time has elapsed between the antibiotic intake and the reaction?
  - Less than an hour after taking the **first dose** of the antibiotic?
  - If it took place during the treatment, how many days after the beginning of treatment?
  - If it took place after the end of treatment, how many days after the end of treatment?



## REMEMBER THAT...

In most people, time is likely to remedy the confirmed allergy to penicillins (e.g., more than half of patients will no longer be allergic to penicillin after 10 years).

In order to find help with differentiating the type of reaction, I can consult the following table or [the interactive tool](#)

Type of allergic reaction*	Immediate reaction	Delayed reaction		
	Type I	Type II	Type III	Type IV
Clinical examples	<ul style="list-style-type: none"> <li>• Anaphylaxis</li> <li>• Angioedema</li> <li>• Bronchospasm</li> <li>• Hypotension</li> <li>• Urticaria</li> </ul>	<ul style="list-style-type: none"> <li>• hemolytic anemia</li> </ul>	<ul style="list-style-type: none"> <li>• Serum sickness</li> <li>• Palpable purpura</li> <li>• Vasculitis</li> </ul>	<ul style="list-style-type: none"> <li>• Maculopapular rash</li> <li>• DRESS</li> <li>• SJS/TEN</li> <li>• AGEP</li> </ul>
Time of onset of symptoms (post-exposure to the drug)	From a few minutes to an hour (can take up to 6 hours)	From a few hours to several days (can take up to 6 weeks for the DRESS)		

\* Adapted from Gell and Coomb classification.



## CAUTION

Any reaction occurring less than one hour after the first dose of the antibiotic suggests an IgE-mediated allergy and could therefore cause an [anaphylactic reaction](#) during re-exposure (the risk of an anaphylactic reaction is very low).



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#### 4. WHAT WERE THE MAIN SIGNS, SYMPTOMS OR IMPAIRMENTS OBSERVED?

In order to find help with differentiating the type of reaction, I can consult the following table or [the interactive tool](#)



##### IDENTIFY...

The different types of impairments which were observed or reported:

- Dermal (e.g., bubbles, pustules, urticaria);
- Gastrointestinal (e.g., vomiting, severe diarrhea);
- Hematologic (e.g., lymphadenopathy, anemia, eosinophilia, lymphocytosis);
- Hepatic (e.g., increased transaminases);
- Renal (e.g., proteinuria, increased urea and/or creatinine);
- Respiratory (e.g., difficulty breathing, bronchospasm, dyspnea, dysphonia, stridor);
- Systemic (e.g. shock, general impairment, hypotension, fever > 38.0 ° C).



##### REMEMBER THAT...

- In children, some clinical presentations (e.g., severe urticaria with arthralgia) are often misdiagnosed as a serum sickness-like reaction.
- Some symptoms that appear after taking antibiotics may suggest intolerance rather than allergy (e.g., amoxicillin-clavulanate diarrhea).



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## 4. WHAT WERE THE MAIN SIGNS, SYMPTOMS OR IMPAIRMENTS OBSERVED?

## a. How severe were cutaneous impairments, if any?



## VERIFY IF...

Did the reaction present a cutaneous manifestation? If so, how severe was the observed or the reported impairment?

- How long did it last?
- Whether there has been desquamation?
- Whether there was associated pruritus?
- Was it more like maculopapular rash or hives?

In order to find help with differentiating the type of reaction, I can consult the following table or [the interactive tool](#)

Distinction	Immediate allergic cutaneous reaction	Delayed allergic cutaneous reaction		
		NON-SEVERE	SEVERE	VERY SEVERE
Clinical examples	Urticaria	Rash	Rash with fever or desquamation	SJS/TEN, DRESS, AGEP
Time of onset of symptoms	Generally <1 hour after taking the 1 <sup>st</sup> dose of the antibiotic	Usually after a few days of treatment	From one hour after taking the antibiotic; in general from a few hours to several days, even up to 6 weeks for DRESS syndrome	
Duration of the reaction	A few hours (<24 hours after stopping the antibiotic) <sup>1</sup>	A few days	Several days to a few weeks	A few weeks to many weeks
Type of lesions and its characteristics	Raised papular lesions	Macular lesions without relief and/or raised papular lesions	Same as non-severe rash + desquamation, pustules, vesicles, purpura with fever or arthralgia, but <b>without</b> DRESS, SJS/TEN, AGEP	Presence of vesicles, gold bubbles or pustules, of very dark color, purpura, desquamation
	Evanescent appearance	Temporarily fade to pressure		
Distribution of lesions	Location is limited to only one part of the body or may extend over several regions (generalized)	Preferred localization and anatomical progression is generally from the trunk to the limbs (depends on the syndrome and the type of lesions)		
Associated pruritus	+++	++	++	+ (DRESS syndrome)
Associated edema	Usually localized and superficial angioedema of the dermis without epidermal change (no scales, no vesicles, etc.) <sup>2</sup>	None	None	Facial edema
Other characteristics	Usually disappears without leaving a trace on the skin and without desquamation	Usually disappears without desquamation and is not accompanied by any other symptom	Fever, impairment of general condition, <b>slight damage</b> to internal organs	Mucous membranes involvement, fever, impairment of the general condition and <b>severe damage</b> to internal organs

## Legend :

1 In the case of pathognomonic urticaria detected in the questionnaire, a duration of more than 48 hours following the discontinuation of the drug generally excludes a type I allergy.

2 When the urticaria is deeper, the lesions sit in the deep dermis and hypodermis. It is then an angioedema or an acute subcutaneous urticaria.



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#### 4. WHAT WERE THE MAIN SIGNS, SYMPTOMS OR IMPAIRMENTS OBSERVED?

b. Did the reaction have any seriousness criteria?



#### IDENTIFY...

Severity criteria, signs, symptoms or important impairments:

- Has the potentially allergic reaction led the patient to emergency or intensive care?
- Did the reaction require treatment? If yes, what was the prescribed treatment and what was the answer?



#### CAUTION

The presence of only one of these signs, symptoms or impairments is sufficient to require an in-depth evaluation or a consultation with the specialized services

TYPE OF IMPAIRMENT	SEVERITY CRITERIA Signs, symptoms and impairments	Immediate reaction		Delayed reaction					
		Type I		Type II	Type III	Type IV			
		Anaphylaxis		Hemolytic anemia	Serum sickness	SJS	TEN	DRESS	AGEP
		Severe	Very severe	Very severe	Severe	Very severe			
Systemic	Shock with or without intubation		✓						
	General condition impairment	✓	✓		✓	✓	✓	✓	✓
	Hypotension	✓	✓					✓	
	Fever > 38.0 °C				✓	✓	✓	✓	✓
Cutaneous	Painful skin					✓	✓	✓	
	Petechia and palpable purpura				✓				
	Mucosal impairment					✓	✓		
	Vesicles, bubbles, pustules							✓	✓
	Desquamation of the skin					✓	✓	✓	✓
	Complete skin detachment (ulcer)					✓	✓	✓	
	% body surface area reached					≤ 10 %	≥ 30 %	≥ 50 %	
Edema	Angioedema (lips, tongue, throat, face)	✓	✓						
	Facial edema							✓	
Respiratory	Dyspnea	✓	✓						✓
	Dysphonia	✓	✓						
	Bronchospasm (or wheezing)	✓	✓						
	Stridor	✓	✓						
Hematological	Urinary eosinophilia							✓	✓
	Lymphocytosis and/or atypical lymphocytosis							✓	
	Lymphadenopathy							✓	
	Anemia			✓				✓	
	Significant increase in CRP (> 100 mg/L) or ferritin (> 500 µg/L)				✓	✓	✓	✓	✓
Other	Joints impairment (arthritis, arthralgia)				✓				
	Renal impairment (↑ proteinuria, urea and creatinine)				✓			✓	
	Hepatic impairment (↑ transaminases)				✓	✓	✓	✓	



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## WHAT YOU NEED TO KNOW... THE CRITERIA FOR REFERRALS TO A SPECIALIST

### Who are the patients who could benefit from specialist consultation and allergic assessment?

For situations where accessibility to an allergist is more difficult, the following criteria could be used to guide an application to specialized services:

#### Immediate allergic reactions (IgE-mediated)

- Patient who has had a suspected anaphylactic reaction, whose history is poorly documented or of unknown etiology (e.g., any unexplained anaphylactic reaction when beta-lactam has been co-administered with several other agents).

#### Very severe delayed allergic reactions

- Patient with a history (suspected or confirmed) of very severe delayed reactions such as DRESS syndrome, SJS / TEN or AGEP.

#### Allergic reactions in a special patients subgroup

- A patient with a history (suspected or confirmed) of allergic reactions to beta-lactam antibiotics (immediate or delayed) if:
  - he is likely to use this type of antibiotic frequently (e.g., patients with recurrent bacterial infections or with COPD with frequent secondary infections, cystic fibrosis or an immune deficiency);
  - he requires treatment for a disease or condition that can only be treated with beta-lactam (e.g., neurosyphilis).
- A pediatric patient with a history (suspected or confirmed) of allergic reactions to beta-lactam antibiotics (immediate or delayed) so that he is not incorrectly labelled allergic and so that he can access the best therapeutic tools.
- A polymedicated patient (e.g., elderly person) with a history (suspected or confirmed) of allergic reactions to beta-lactam antibiotics (immediate or delayed) who is at a higher risk of drug interactions or in whom safe options are more limited (e.g., patient who is currently on medications that prolong the QT interval).

#### Multiple allergy

- Patient with a history of allergic reactions to beta-lactams and at least one other class of antibiotics, specifically patients with allergies to:
  - penicillins and quinolones;
  - penicillins and macrolides;
  - penicillins and trimethoprim-sulfamethoxazole.



## REMEMBER THAT...

Upon reception of the diagnosis following a consultation with the specialized services, the complete information on the drug allergy should be updated in the patient's medical record or in a place reserved for this purpose in the computerized/electronic files (EHR or DMÉ) and minimally included in the following documents and databases:

- Consultation report for the attending physician;
- Pharmacological record (hospital or community);
- Medical records service of the hospital.

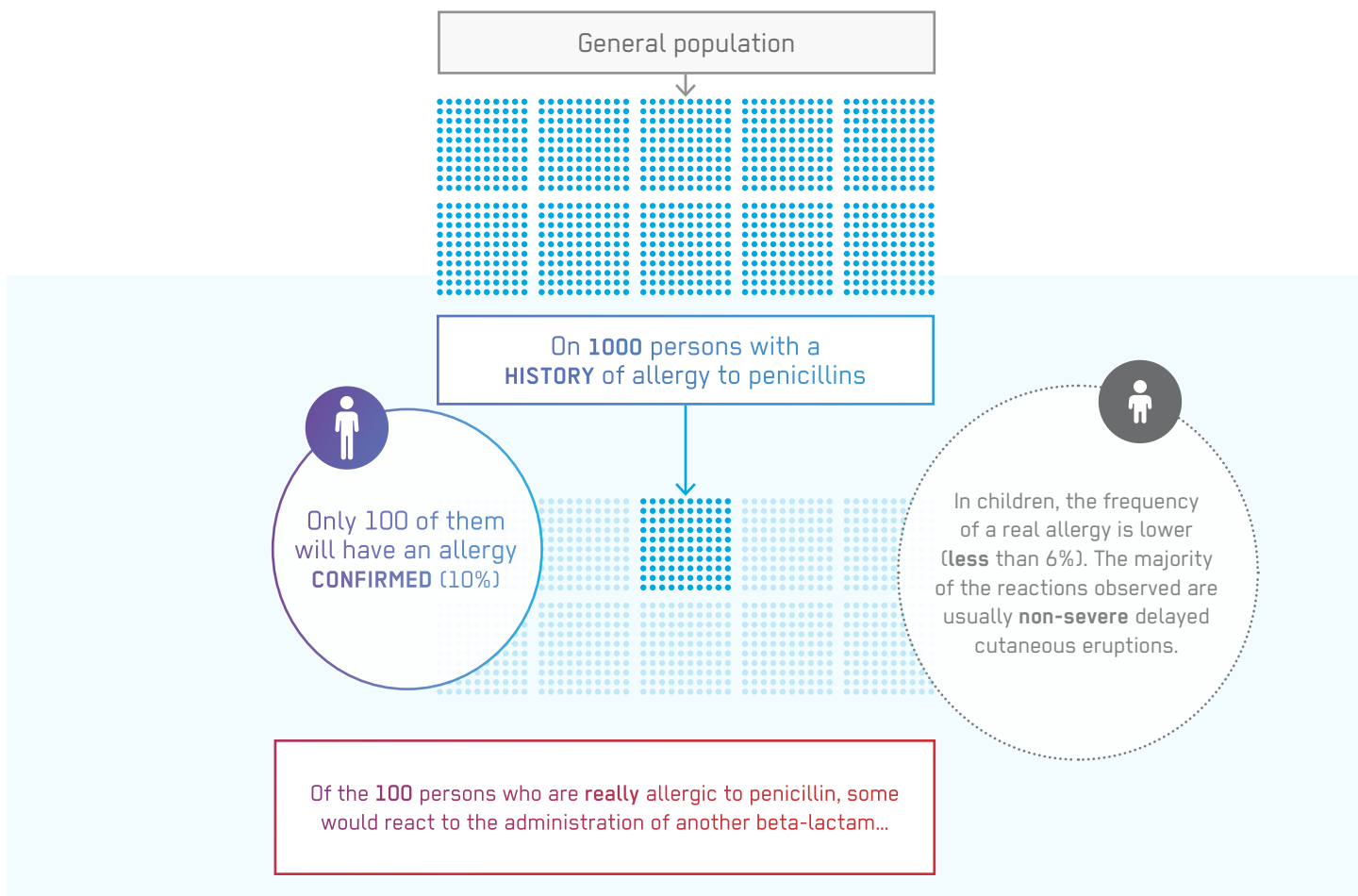


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## 5. WHAT ARE THE RISKS ASSOCIATED WITH THE RE-EXPOSURE TO A BETA-LACTAM?



**Remarks :** The figures are presented for reference only. They are supported by data from the scientific literature and are linked to several guidelines.

**Legend :**

\* Similarities between penicillins and cephalosporins were assessed for structural properties (R1 side chain) and physicochemical properties (e.g., pKa, charge, polarity, hydrophobicity, hydrogen bond donor/acceptor, etc.). For more information, click [here](#).

## 6. IN PRIMARY CARE, WHAT IS THE PROCESS TO BE FOLLOWED AND THE NECESSARY PREREQUISITES TO PERFORM DRUG PROVOCATION TESTS IN THE CASE OF PATIENTS WITH A PRIOR HISTORY OF IGE-MEDIATED (TYPE I) REACTION?



### WHAT YOU NEED TO KNOW... DRUG PROVOCATION TESTS

- Drug provocation tests must be performed under medical supervision, by trained personnel and in care settings equipped with resuscitation equipment.
- Optimally, the administration of the antibiotic should be done in two steps:
  - **10%** of the total dose (a delay of 30 minutes\* is recommended before the administration of the 2<sup>nd</sup> dose);
  - **90%** of the total dose.
- A patient observation period of **60 minutes** after the last dose is advised.

\* regardless of the route of administration (oral or injectable)



### CAUTION

- A 3-step procedure with 60-minute intervals starting at 1% of the total dose is desirable for patients with a history of anaphylaxis.
- Drug provocation tests are contraindicated in the cases of very severe allergic reactions (e.g., anaphylactic shock, SJS / TEN, DRESS, AGEP).
- A verbal consent from the patient should be obtained and documented on file (or as per the terms of each facility).
- In the case of a delayed allergic reaction, late effects (usually an itchy eruption) may occur within days after the test (it is important to advise the patient).



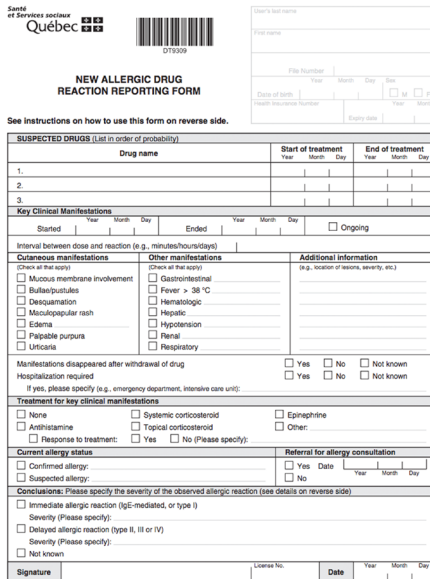
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## 7. WHAT MEASURES ARE TO BE TAKEN AFTER THE ADMINISTRATION OF A NEW BETA-LACTAM TO A PATIENT WHO HAS A SUSPECTED OR CONFIRMED PENICILLIN ALLERGY?

### In case of allergic reaction:



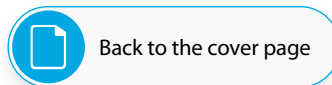
- Stop the antibiotic administration and treat the reaction as needed.\*
- Complete the declaration form for a new drug allergy reaction ([French: AH-707 DT-9308](#)) ([English: AH-707A DT-9309](#)).
- Update the complete information on drug allergy status in, at least, the following document and databases:
  - Patient's medical record or in a designated area for this purpose in computerized/ electronic files (electronic health record system (EHR) such as Cristal net or electronic medical file (DMÉ));
  - Request for consultation with the medical specialist or consultation report destined to the attending physician;
  - Pharmacological record (hospital or community care);
  - Medical records service of the hospital.
- Clearly inform the patient about his diagnosis, his type of reaction, and the name of the suspected drug.
- Assess the need for consultation with specialized services.

\* If necessary, consult the clinical criteria for the diagnosis of anaphylaxis.

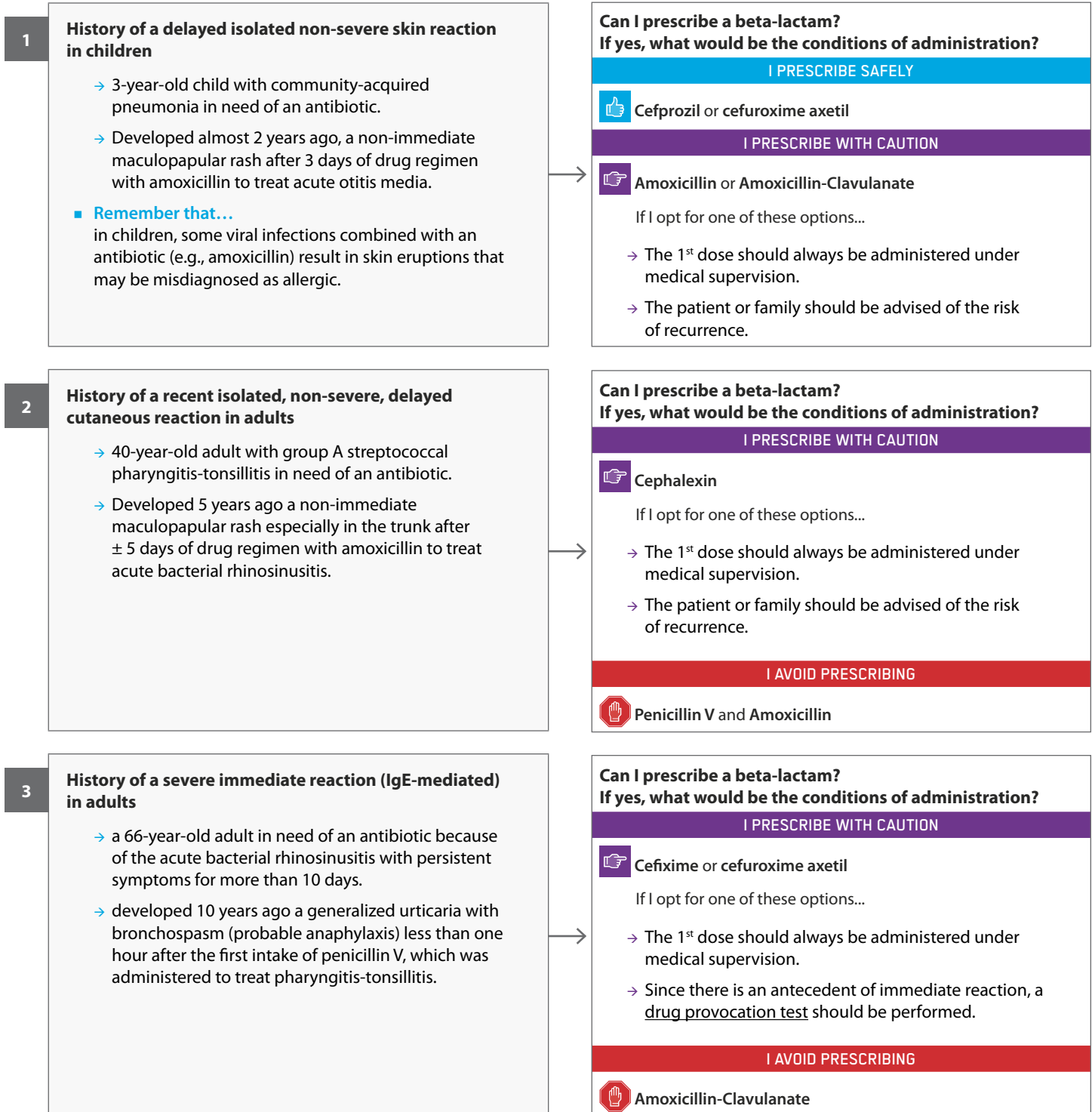
### If there is an antibiotic tolerance or an adverse effect:

#### Clearly document the observed reaction:










- In the patient's medical record;
- In a place reserved for this purpose in computerized/electronic files.



The clinical cases are provided here for guidance and do not replace the professional's judgment. They must be used as a decision support tool only.



## LEGEND

 VERIFY IF...  IDENTIFY... Sets of important elements to check or identify during the clinical examination.	 Administration without special precautions.
 REMEMBER THAT... Reminder of relevant information that may assist the diagnostic process.	 Administration possible with certain precautions: according to the history of the initial reaction and to the awareness of the clinician and patient or his family regarding low risk level.
 WHAT YOU NEED TO KNOW... Information which is relevant and necessary for optimal patient management.	 Administration possible with some precautions <b>ONLY</b> for the specified conditions.
 CAUTION Zones of vigilance or special attention to be paid during the clinical evaluation.	 Administration generally not recommended: to opt rather for an antibiotic of a class other than that of beta-lactams and obtain a consultation with the <u>specialized services</u> .

## ABBREVIATIONS

AGEP: acute generalized exanthematous pustulosis,  
 COPD: chronic obstructive pulmonary disease,  
 DCI: dossier clinique informatisé,  
 DMÉ: dossiers médicaux électroniques,  
 DRESS: drug reaction with eosinophilia and systemic symptoms,

EHR: electronic health record system,  
 Rash: maculopapular rash (also known as maculopapular eruption),  
 SJS: Stevens–Johnson *syndrome*,  
 TEN: *toxic epidermal necrolysis*.

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It is derived from the *Avis sur la standardisation des pratiques relatives aux allergies aux bêta-lactamines* et son *Addenda* (Notice on the Standardization of practices regarding beta lactam allergies and its Addendum).

These documents are available [here](#).

#### **Project team**

##### **Authors**

Geneviève Robitaille, Ph. D.

Fatiha Karam, Ph. D.

##### **Scientific coordination**

Mélanie Tardif, Ph. D.

##### **Scientific leadership**

Sylvie Bouchard, B. Pharm., D.P.H., M. Sc., M.B.A.

##### **Knowledge transfer team**

Renée Latulippe, M. A., scientific coordinator

Mélanie Samson, Ph. D., scientist-practitioner

Amina Yasmine Acher, M. A., graphic designer

##### **Advisory committee**

Philippe Bégin, M. D., Ph. D., FRCPC, allergist-immunologist, Sainte-Justine University Hospital Center and University Hospital of Montreal; associate clinical professor, University of Montreal, Montreal, Quebec.

Marie-Dominic Breault, M. D., emergency physician, Integrated Health and Social Services Center (CISSS), Gaspésie-Îles-de-la-Madeleine, Quebec.

Jonathan Lacombe-Barrios, M. D., FRCPC, allergist-immunologist, Sainte-Justine University Hospital Center, professor, department of pediatrics, Faculty of Medicine, University of Montreal, Montreal, Quebec.

Isabelle Levasseur, nurse practitioner, GMF Laval (UMF of Cité-de-la-Santé, Laval), Quebec.

Hélène Paradis, B. Pharm., M. Sc., pharmacist; chief of the pharmacy department of the Integrated Health and Social Services Center (CIUSSS) of the West Island of Montreal, Montreal, Quebec.

Matthieu Picard, M. D., FRCPC, allergist-immunologist, Maisonneuve-Rosemont Hospital, assistant clinical professor, University of Montreal, Montreal, Quebec.

Frédéric Poitras, B. Pharm., community pharmacist; lecturer, Faculty of Pharmacy, Laval University, Quebec, Quebec.

##### **Participants in the expanded consultation (other than Advisory Committee members)**

Cybèle Bergeron, M. D., FRCPC, pediatrician-infectiologist, University Hospital of Sherbrooke, Sherbrooke, Quebec.

Luc Bergeron, B. Pharm, pharmacist and clinical professor, University Hospital of Quebec - Laval University, Quebec, Quebec.

Michel Cauchon, M. D., family physician, Maizerets family medicine unit; professor, Faculty of Medicine, department of family medicine and emergency medicine, Laval University, Quebec, Quebec.

Sylvain Couture, M. D., family doctor, in private practice (Quebec).

Jean-Philippe Drolet, M. D., FRCPC, allergist-immunologist, pediatrician, University Hospital of Quebec - Laval University, Quebec, Quebec.

Rémi Gagnon, M. D., FRCPC, allergist-immunologist and chief of the allergy and immunology department at the Clinic of the University Hospital of Quebec, Laval University, Quebec City, Quebec; president of the Association of Allergists and Immunologists of Quebec (AAIQ).

Dany Harvey, M. D., FRCPC, pediatrician, Carrefour de santé de Jonquière, Saguenay-Lac St-Jean, Quebec.

Allison Kukhta, M. D., FRCPC, allergist-immunologist, pediatrician, Vallée-de-l'Or Health and Social Services Center, Val-d'Or, Quebec.

Marc Lebel, M. D., FRCPC, pediatrician-infectiologist at the University Hospital of Sainte-Justine and associate clinical professor, department of pediatrics, University of Montreal, Montreal, Quebec.

Chantal Lemire, M. D., FRCPC, pediatric clinical allergist-immunologist, Estrie Integrated Center for Health and Social Services - Sherbrooke University Hospital Center, Sherbrooke, Quebec.

Nicole Le Saux, M. D., FRCPC, pediatrician-infectiologist, Children's Hospital of Eastern Ontario (CHEO) research associate professor, Faculty of Medicine, University of Ottawa, Ottawa, Ontario.

Pierre-Claude Poulin, M. D., FRCPC, pediatrician, Integrated Health and Social Services Center of Chaudière-Appalaches, Beauce sector, St-Georges (Quebec).

Audrey Vachon, B. Pharm, M. Sc., pharmacist, University Institute of Cardiology and Pulmonology of Quebec, Quebec City, Quebec; clinical professor, Faculty of Pharmacy, Laval University, Quebec, Quebec.

#### **Siège social**

2535, boulevard Laurier, 5<sup>e</sup> étage

Québec (Québec) G1V 4M3

418 643-1339

#### **Bureau de Montréal**

2021, avenue Union, bureau 10.083

Montréal (Québec) H3A 2S9

514 873-2563

[inesss.qc.ca](http://inesss.qc.ca)



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